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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/000,213	11/14/2001	Brenda F. Baker	RTS-0327	1275

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EXAMINER
GIBBS, TERRA C

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 03/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/000,213	Applicant(s) BAKER ET AL.	
	Examiner Terra C. Gibbs	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-20* is/are pending in the application.

4a) Of the above claim(s) *19 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3
4)☐ Interview Summary (PTO-413) Paper No(s) _____
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other

DETAILED ACTION

This Office Action is a response to the Election filed 2/13/03, in Paper No. 5.

Claims 1-20 are pending in the instant application.

Claim 3 has been canceled. Claim 1 has been amended. Claims 19 and 20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 5.

Claims 1, 2, and 4-18 have been examined to the extent they read on the elected subject matter.

Election/Restrictions

Applicant's election with traverse of Group I (claims 1-18) and SEQ ID NO:3, in Paper No. 5 is acknowledged. The traversal is on the ground(s) that all of the claims are related to the single concept of modulating the expression of vitamin D nuclear receptor. Further, Applicant argues that a search of literature relating to vitamin D nuclear receptor would clearly reveal art relating to all of the claims, and therefore would not place an undue burden on the examiner. This is not found persuasive because, as argued in the restriction requirement (Paper No. 4), the compound of Group I may be used in another method other than the methods of Groups II-V. Therefore, a search for the compound of Group I will not encompass all of the art relevant to the methods of Groups II-V. With regard to the relationship of the claims as product, process of making and process of using, the argument is not persuasive because restriction is proper regardless of whether the claims are related as product and process of making or product, process

of making and process of using. Where claims are drawn to a product, process of making and process of using, restriction may be required where the process of making and product made are distinct according to the guidelines set forth in MPEP 806.05(f) (see MPEP 806.05(i)), as was demonstrated for the product and process of using of the instant application.

The requirement is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

Foreign Patent Document WO 01/38393, listed as reference AP in the Information Disclosure Statement has not been considered since an English translation was not provided.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The term "compound" in claims 1, 11, 12 and 13 is a relative term which renders the claim indefinite. The term "compound" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Replacement with the language "an oligonucleotide" would overcome the instant rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting the expression of vitamin D nuclear receptor in cells (*in vitro*) using an oligonucleotide 8 to 50 nucleotides in length that targets and inhibits the expression of vitamin D nuclear receptor, does not reasonably provide enablement for a method of inhibiting the expression of vitamin D nuclear receptor in cells (*in vivo*) or method of treating human having a disease or condition associated with vitamin D nuclear receptor using any compound 8 to 50 nucleotides in length that targets and inhibits the expression of vitamin D nuclear receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 15-18 are drawn to an antisense-based therapy in an animal having a disease or condition associated with vitamin D nuclear receptor via a compound 8 to 50 nucleotides in length that targets and inhibits the expression of vitamin D nuclear receptor.

The instant invention specification provides methodologies for antisense inhibition of human vitamin D nuclear receptor in cell culture (see Examples 9-15 and Table I).

Chatterjee, M. (Mutation Research, 2001 Vol. 475:69-88) assert that although many advances have been made in the past decade, much still remains to be learnt about vitamin D and its metabolites (see page 84, last paragraph).

Hewison et al. (Journal of Immunology, 2996 Vol. 156:4391-4400) assert that although the vitamin D receptor expression is widespread, it is not universal and many questions remain to be resolved regarding the function of the vitamin D receptor (see page 4398, last paragraph).

The assertions of Hewison et al. indicate that further research is required in the art to understand the function of the vitamin D nuclear receptor. Further assertions by Chatterjee, M. indicate that further research is required in the art before vitamin D nuclear receptor antisense oligonucleotides can be employed as a potential therapeutic means.

Furthermore, the unpredictability of the art of antisense therapy in general adds to the lack of enablement for the current invention. For example, Branch (TIBS, February 1998 Vol. 23, pages 45-50) addresses the unpredictability and the problems faced in the antisense art with the following statements: "Antisense molecules and ribozymes capture the imagination with their promise or rational drug design and exquisite specificity. However, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven."; "To minimize unwanted non-antisense effects, investigators are searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to attack. This is a challenging quest."; "However, their unpredictability confounds research application of nucleic acid reagents."; "Non-antisense effects are not the only impediments to rational antisense drug design. The internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules."; "Years of investigation can be required to figure out what an 'antisense' molecule is actually doing...."; "Because knowledge of their underlying mechanism is typically acting, non-antisense effects muddy the waters."; "Because biologically

active compounds generally have a variety of effects, dose-response curves are always needed to establish a compounds primary pharmacological identity. Antisense compounds are no exception. As is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curve of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range."; "Because it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells."; "Binding is the rare exception rather than the rule, and antisense molecules are excluded from most complementary sites. Since accessibility cannot be predicted, rational design of antisense molecules in not possible."; and, "The relationship between accessibility to oligonucleotide (ODN) binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored...It is not yet clear whether *in vitro* screening techniques...will identify ODN's that are effective *in vivo*."

Jen et al. (Stem Cells, 2000, Vol. 18:307-319) discuss antisense-based therapy and the challenges that remain before the use of antisense becomes routine in a therapeutic setting. Jen et al. discuss the advances made in the art but also indicate that more progress needs to be made in the art. In the conclusion of their review, Jen et al. assert, "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." It is also stated, "The key challenges to this field have been outlined above. It is clear that they will have to be solved if this approach to specific antitumor therapy is to become a useful treatment approach. A large number of diverse and talented groups are working

on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." It is clear from Jen et al. that the state of the art of antisense is unpredictable and those highly skilled in the art are working towards making the art of antisense therapy more predictable but have many obstacles to overcome.

Dias et al. (European Journal of Pharmaceutics and Biopharmaceutics, 2002 Vol. 54:263-269) addresses the limitations of antisense-based therapy. Dias et al. state, "Even though the antisense strategy is widely employed currently, it has certain defined limitations. Although it is relatively easy to synthesize phosphodiester oligonucleotides, these cannot *[emphasis added]* be used as drugs due to their propensity to be easily degraded by cellular nucleases" (see page 263, first column). Dias et al. further discuss that different methods, such as electroporation, microinjection or the binding to particular peptides with membrane translocation properties have been developed to overcome internalization problems, however these methods are easily applied in cultured cells, but may or may not be useful in *in vivo* systems (see page 263, second column).

In view of the unpredictability in the art, the specification as filed does not provide adequate guidance or examples that would show by correlation how one skilled in the art would practice the claimed invention over the scope claimed without having to engage in trial and error or undue experimentation. The specification as filed contemplates the therapeutic use of vitamin D nuclear receptor antisense in a broad range of divergent/unrelated diseases (e.g. a cancer or a developmental disorder). However, the instant specification does not show any specific link between vitamin D nuclear receptor and any specific disease or condition such that treatment with vitamin D nuclear receptor antisense would be an apparent treatment option. It is unclear how the specific cell culture (*in vitro*) data is correlated with or representative of treatment to

wide range of diseases or conditions (*in vivo*) with any vitamin D nuclear receptor antisense. It is also unclear how any vitamin D nuclear receptor antisense will treat any one of the range of diseases or conditions recited where no specific guidance (i.e. specific mode of treatment, delivery route, tissue specificity, etc.) is provided.

The specification does not provide particular guidance or particular direction for the treatment of a disease or condition associated with vitamin D nuclear receptor in an animal. The specification does not provide guidance for the delivery of antisense compounds into the target organ and target cells in an animal in quantity sufficient to inhibit vitamin D nuclear receptor expression. While the specification provides guidance to addressing antisense compound administration to cells in culture, the specification provides no particular nexus between the inhibition of vitamin D nuclear receptor *in vivo* for the treatment of a disease or condition associated with vitamin D nuclear receptor in an animal, as contemplated by the specification. The specification provides no particular guidance of direction for addressing the problems of targeting, permanence and quantity of expression of the gene in question, immunogenicity, etc. for nucleic acid/antisense targeting vitamin D nuclear receptor in an animal. The specification provides no particular guidance or direction for the treatment of an animal having a disease or condition associated with vitamin D nuclear receptor using the vitamin D nuclear receptor antisense oligonucleotides of the claimed invention.

Therefore, in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, one of ordinary skill in the art at the time of the invention would have required an undue amount of experimentation to make and use the claimed invention commensurate with the full scope of the claims. Due to the lack of specific

guidance in the specification as filed and the lack of correlation between targeting and inhibiting the expression of vitamin D nuclear receptor in cell culture and *in vivo*, one of skill in the art would require specific guidance to practice the current invention. The current specification does not provide such guidance to target and inhibit the expression of vitamin D nuclear receptor *in vivo* and one of skill in the art would be required to perform trial and error or undue experimentation. The quantity of experimentation required to practice the invention over the scope claimed would include the de novo determination of how to engineer and deliver an antisense targeting vitamin D nuclear receptor such that any disease or condition (e.g. a cancer or a developmental disorder) associated thereto would be treated to any degree, particularly, in view of the obstacles needed to overcome to use antisense therapies as exemplified in the references discussed above. It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Accordingly, limiting the scope of the claimed invention to method of inhibiting the expression of vitamin D nuclear receptor in cells (*in vitro*) using an oligonucleotide 8 to 50 nucleotides in length that targets and inhibits the expression of vitamin D nuclear receptor is proper.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4, 5, 11 and 15 are rejected under 35 USC 102(b) as being anticipated by Hmama et al. (Journal of Experimental Medicine, 1999 Vol. 190:1583-1594).

Claims 1, 2, 4 and 5 are drawn to a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding vitamin D nuclear receptor; wherein said compound specifically hybridizes with said nucleic acid molecule encoding vitamin D nuclear receptor and inhibits the expression of vitamin D nuclear receptor; wherein the compound is an antisense oligonucleotide; wherein the antisense oligonucleotide comprises one modified internucleoside linkage; wherein the modified internucleoside linkage is a phosphorothioate linkage. Claim 11 is drawn to a compound 8 to 50 nucleobases in length that specifically hybridizes with at least an 8-nucleobase portion of an active site on a nucleic acid encoding vitamin D nuclear receptor. Claim 15 is drawn to a method of inhibiting the expression of vitamin D nuclear receptor in cells using a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding vitamin D nuclear receptor.

Hmama et al. disclose a 21-base paired phosphorothioate antisense oligonucleotide targeting the start codon of the human vitamin D nuclear receptor (see page 1585, sense and antisense oligonucleotides). Hmama et al. also disclose that the antisense oligonucleotide was expressed in THP-1 cells and inhibited vitamin D nuclear receptor protein expression (see Figure 6A). Hmama et al. further disclose that vitamin D nuclear receptor is required for D_3-iunduced expression of CD14 mRNA and thus vitamin D nuclear receptor signaling has a novel role in myeloid cell differentiation.

Therefore, Hmama et al. anticipate the current invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 6-10 and 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hmama et al. (Journal of Experimental Medicine, 1999 Vol. 190:1583-1594) in view of Baracchini et al. [U.S. Patent No. 5801154] and Fritz et al. (Journal of Colloid and Interface Science, 1997 Vol. 195:272-288).

Claims 1, 6-10 are drawn to a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding vitamin D nuclear receptor; wherein said compound specifically hybridizes with said nucleic acid molecule encoding vitamin D nuclear receptor and inhibits the expression of vitamin D nuclear receptor; wherein the antisense oligonucleotide comprises at least one modified sugar moiety; wherein the sugar moiety is a 2'-O-methoxyethyl sugar moiety; wherein the antisense oligonucleotide comprises at least one modified nucleobase; wherein the modified nucleobase is a 5-methylcytosine; wherein the antisense oligonucleotide is a chimeric oligonucleotide. Claims 12-14 are drawn to a composition comprising a compound 8 to 50

nucleobases in length targeted to a nucleic acid molecule encoding vitamin D nuclear receptor and a pharmaceutically acceptable carrier or diluent, further comprising a colloidal dispersion system.

Hmama et al. teach a 21-base paired phosphorothioate antisense oligonucleotide targeting the start codon of the human vitamin D nuclear receptor (see page 1585, sense and antisense oligonucleotides). Hmama et al. also teach that the antisense oligonucleotide was expressed in THP-1 cells and inhibited vitamin D nuclear receptor protein expression (see Figure 6A). Hmama et al. further teach that vitamin D nuclear receptor is required for D_3-iunduced expression of CD14 mRNA and thus vitamin D nuclear receptor signaling has a novel role in myeloid cell differentiation.

Hmama et al. do not teach wherein the antisense oligonucleotide comprises at least one modified sugar moiety; wherein the sugar moiety is a 2'-O-methoxyethyl sugar moiety; wherein the antisense oligonucleotide comprises at least one modified nucleobase; wherein the modified nucleobase is a 5-methylcytosine; wherein the antisense oligonucleotide is a chimeric oligonucleotide; and a composition comprising the compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding vitamin D nuclear receptor and a pharmaceutically acceptable carrier or diluent, further comprising a colloidal dispersion system.

Baracchini et al. teach modified or substituted oligonucleotides are often preferred over native forms because of desirable properties such as enhanced cellular uptake, enhanced affinity for nucleic acid target and increased stability in the presence of nucleases. Baracchini et al. further teach antisense oligonucleotides with phosphorothioate-modified backbones (see column 6, line 37)... with at least one modified sugar moiety and a modified 2'-O-methoxyethyl sugar

moieties (see Table I)... with modified nucleobases, such as 5-methylcytosine (see column 7, lines 15-25). Baracchini et al. finally teach an antisense oligonucleotide as a chimeric oligonucleotide (see column 8, lines 12-19)

Fritz et al. teach a composition comprising an antisense oligonucleotide and a pharmaceutically acceptable carrier or diluent comprising a colloidal dispersion system. Fritz et al. further teach that oligonucleotides, in combination with steric stabilizers, exhibit high colloidal stability with low toxic side effects as required for biological experiments in cell culture and *in vivo* (see page 287, last paragraph).

It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to modify the antisense nucleic acids targeting vitamin D nuclear receptor taught by Hmama et al. with various modifications and substitutions such as a modified internucleoside linkage, a modified sugar moiety, a 2'-O-methoxyethyl sugar moiety, a modified nucleobase, a 5-methylcytosine, a chimeric oligonucleotide and a composition comprising a compound 8 to 50 nucleobases in length targeted to a nucleic acid molecule encoding vitamin D nuclear receptor and a pharmaceutically acceptable carrier or diluent, further comprising a colloidal dispersion system, following the methods of Baracchini et al. and Fritz et al. with a reasonable expectation of success. One of ordinary skill in the art would have been motivated to modify the antisense oligonucleotides since the prior art has taught the desirability of such oligonucleotides are often preferred over native forms because of enhanced cellular uptake, enhanced affinity for nucleic acid target, increased stability in the presence of nucleases and the exhibition of high colloidal stability with low toxic side effects as required for biological

experiments (see Baracchini et al., column 3, lines 17-41, column 6, line 37 and Table I and Fritz et al. page 287, last paragraph)

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (703) 306-3221. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 746-8693 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

tcg
March 6, 2003

Ram R. Shukla

RAM R. SHUKLA, PH.D
PATENT EXAMINER